General

Guideline Title

Brain metastases.

Bibliographic Source(s)

Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, Heimans J, Hildebrand J, Hoskin P, Kalljo M, Krauseneck P, Marosi C, Siegal T, Vecht C. Brain metastases. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 437-45. [59 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, Heimans J, Hildebrand J, Hoskin P, Kalljo M, Krauseneck P, Marosi C, Siegal T, Vecht C. EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. Eur J Neurol 2006 Jul;13(7):674-81.

Recommendations

Major Recommendations

The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

Diagnosis

- When neurological symptoms and/or signs develop in a patient with known systemic cancer, brain metastases must always be suspected. Careful medical history and physical examination with emphasis on the presence/activity of the systemic disease and the general physical condition (estimation of the performance status) are recommended (GPP).
- Computed tomography (CT) is inferior to magnetic resonance imaging (MRI) (Level B), but it is sufficient when it shows multiple brain metastases.
- Contrast-enhanced MRI is indicated when: (a) surgery or radiosurgery are considered, one or two metastases on contrast-enhanced CT and a Karnofsky Performance Status (KPS) ≥70 (refer to Table 30.1 in the original guideline document); (b) contrast-enhanced CT is negative but the history is strongly suggestive of the presence of brain metastases in a patient with established malignant disease; and (c) CT is not conclusive to eliminate non-neoplastic lesions (abscesses, infections, demyelinating diseases, vascular lesions) (GPP).
- Diffusion MRI is useful for the differential diagnosis of ring-enhancing lesions (Level C).
- Electroencephalography (EEG) is indicated where there is suspicion of epilepsy, but there remains clinical uncertainty (GPP).

- Tissue diagnosis (by stereotactic or open surgery) should be obtained when: (a) the primary tumor is unknown, (b) the systemic cancer is well controlled and the patient is a long-term survivor, (c) lesions on MRI do not show the typical aspect of brain metastases, (d) there is clinical suspicion of an abscess (fever, meningism) (Level B). In patients with unknown primary tumor, CT of the chest/abdomen and mammography are recommended, but a further extensive evaluation is not appropriate in the absence of specific symptoms or indications from the brain biopsy (GPP). Fluorine-18-labelled deoxyglucose positron-emission tomography (FDG PET) can be useful for detecting the primary tumor (GPP). The histopathologic studies on the brain metastasis may provide valuable information in indicating a likely organ of origin and guiding further specialized diagnostic work-up: in this regard immunohistochemical staining to detect tissue-, organ-, or tumour-specific antigens is useful (GPP).
- Cerebrospinal fluid (CSF) cytology and contrast enhanced MRI of the spine are needed when the coexistence of a carcinomatous meningitis is suspected (GPP).

Supportive Care

- Dexamethasone is the corticosteroid of choice and twice-daily dosing is sufficient (GPP). Starting doses should not exceed 4 to 8 mg per day, but patients with severe symptoms, including impaired consciousness or other signs of increased intracranial pressure, may benefit from higher doses (≥16 mg/day [Level B]). An attempt to reduce the dose should be undertaken within 1 week of initiation of treatment; if possible, steroids should be weaned off within 2 weeks. If complete weaning off is not possible, the lowest possible dose should be looked for. Asymptomatic patients do not require steroids. Steroids may reduce the acute side effects of radiation therapy. All recommendations are Good Practice Points.
- Antiepileptic drugs (AEDs) should not be prescribed prophylactically (Level A). In patients who suffer from epileptic seizures and need a concomitant treatment with chemotherapeutics, enzyme-inducing antiepileptic drugs (EIAEDs) should be avoided (Level B).
- In patients with venous thromboembolism, low-molecular-weight heparin is effective and well tolerated for both initial therapy and secondary prophylaxis (Level A). A duration ranging from 3 to 6 months is recommended (GPP). Prophylaxis in patients undergoing surgery is recommended (Level B).

Treatment of Single Brain Metastasis

- Surgical resection should be considered in patients with single brain metastasis in an accessible location, especially when the size is large, the mass effect is considerable and an obstructive hydrocephalus is present (GPP). Surgery is recommended when the systemic disease is absent/controlled and the Karnofsky Performance score is 70 or more (Level A). When the combined resection of a solitary brain metastasis and a non-small-cell lung carcinoma (stage I and II) is feasible, surgery for the brain lesion should come first, with a maximum delay between the two surgeries not exceeding 3 weeks (GPP). Patients with disseminated but controllable systemic disease (i.e., bone metastases from breast cancer) or with a radioresistant primary tumour (melanoma, renal cell carcinoma) may benefit from surgery (GPP). Surgery at recurrence is useful in selected patients (Level C).
- Stereotactic radiosurgery (SRS) should be considered in patients with metastases of a diameter of ≤3–3.5 cm and/or located in eloquent cortical areas, basal ganglia, brain stem or with comorbidities precluding surgery (Level B). SRS may be effective at recurrence after prior radiation (Level B).
- Whole-brain radiotherapy (WBRT) alone is the therapy of choice for patients with active systemic disease and/or poor performance status and should employ hypofractionated regimens such as 30 Gy in 10 fractions or 20 Gy in five fractions (Level B). For patients with poor performance status supportive care only can be employed (GPP).
- Following surgery or radiosurgery, in case of absent/controlled systemic disease and Karnofsky Performance score of 70 or more, one can either withhold adjuvant WBRT if close follow-up with MRI (every 3–4 months) is performed or deliver early WBRT with fractions of 1.8–2 Gy to a total dose of 40–55 Gy to avoid late neurotoxicity (GPP).

Treatment of Multiple Brain Metastases

- In patients with up to three brain metastases, good performance status (KPS of 70 or more) and controlled systemic disease, SRS is an alternative to WBRT (Level B), while surgical resection is an option in selected patients (Level C).
- In patients with more than three brain metastases WBRT with hypofractionated regimens is the treatment of choice (Level B), whereas for patients with poor performance status supportive care only can be employed (GPP).

Chemotherapy

- Chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumours, like small-cell lung cancers, lymphomas, germ cell tumours and breast cancers, especially if asymptomatic, chemo-naive patients, or if an effective chemotherapy schedule for the primary is still available (GPP).

Targeted Therapies

- Targeted therapies can be employed in patients with brain metastases recurrent after radiation therapy (GPP).

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point When sufficient evidence for recommendations A–C was not available, the task force considered a recommendation to be a

'Good Practice Point' if agreed by all members of the task force.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Brain metastases

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Neurological Surgery

Neurology

Oncology

Radiation Oncology

Intended Users

Physicians

Guideline Objective(s)

- To establish evidence-based guidelines in regard to the management of patients with brain metastases
- To identify areas where there are still controversies and clinical trials are needed

Target Population

Patients with brain metastases

Interventions and Practices Considered

Diagnosis/Evaluation

1. Medical history and physical examination
2. Computed tomography (CT) or magnetic resonance imaging (MRI)
3. Contrast-enhanced or diffusion MRI
4. Electroencephalogram (EEG)
5. Tissue diagnosis/histopathologic studies (by stereotactic or open surgery) if needed
6. Fluorodeoxyglucose positron-emission tomography (FDG PET) for detecting the primary tumor
7. CT of the chest/abdomen and mammography
8. Cerebrospinal fluid cytology, if indicated

Management/Treatment

1. Surgical resection
2. Stereotactic radiosurgery (SRS)
3. Whole-brain radiotherapy (adjuvant or alone)
4. Chemotherapy
5. Targeted therapies
6. Supportive care (dexamethasone, antiepileptic drugs in patients with seizures, low-molecular-weight heparin in patients with venous thromboembolism)

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Effectiveness of treatment in improving median and overall survival, local tumor control, and functional independence and reducing relapse rate

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The task force members searched the following databases: the Cochrane Library to date; Medline–Ovid (January 1966 to date); Medline–ProQuest; Medline-EIFL; EMBASE–Ovid (January 1990 to date); CancerNet; Science Citation Index (ISI). They used specific and sensitive keywords, as well as combinations of keywords, and publications in any language of countries represented in the task force. The task force members also collected guidelines from national and European multidisciplinary neuro-oncological societies and groups (from Italy, France, Netherlands, Germany, and the UK). Moreover, they performed an investigation (by e-mail questionnaire) regarding the views of members of the task force on several critical issues, reflecting the different national situations (10 countries) and specializations (11 neurologists, one neurosurgeon, one radiation oncologist, and one medical oncologist).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The scientific evidence of papers collected from the literature was evaluated and graded according to European Federation of Neurological Societies (EFNS) Guidelines (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The scientific evidence of papers collected from the literature was evaluated and graded according to European Federation of Neurological Societies (EFNS) Guidelines, and recommendations were given according to the same paper (see the "Availability of Companion Documents" field). When sufficient evidence for recommendations A–C was not available, the task force considered a recommendation to be a 'Good Practice Point' (GPP) if agreed by all members of the task force. When analyzing results and drawing recommendations, at any stage the differences were resolved by discussions.

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point When sufficient evidence for recommendations A–C was not available, the task force considered a recommendation to be a 'Good Practice Point' if agreed by all members of the task force.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and treatment of brain metastases

Potential Harms

- Double or triple doses of gadolinium-based contrast agents are better than single doses, but increasing the dose may lead to an increased number of false-positive findings.
- Side effects from chronic *dexamethasone* administration, including myopathy, are frequent and contribute to disability.
- Subtherapeutic levels of *anticonvulsants* were extremely common and the severity of side effects appeared to be higher (20% to 40%) in brain tumor patients than in the general population receiving anticonvulsants, probably because of drug interactions. Phenytoin, carbamazepine, and phenobarbital stimulate the cytochrome P450 system and accelerate the metabolism of corticosteroids and chemotherapeutic agents such as nitrosoureas, paclitaxel, cyclophosphamide, topotecan, irinotecan, thiotepa, adriamycin, and methotrexate, and thus reduce their efficacy.
- Acute (early) and chronic (late) complications following *radiosurgery* are reported in 10% to 40% of patients, serious complications being rare. Acute reactions (due to oedema) occur more often within 2 weeks of treatment, and include headache, nausea and vomiting, worsening of preexistent neurological deficits, and seizures. These reactions are generally reversible with steroids. Chronic complications consist of haemorrhage and radionecrosis (1% to 17%), requiring reoperation in up to 4% of patients.
- *Surgery* for brain metastases can be complicated by leptomeningeal dissemination (LMD), especially in patients with posterior fossa metastases.
- *Whole-brain radiotherapy (WBRT)* alone may cause nausea, vomiting, headache, fever and transient worsening of neurological symptoms in the initial phase of therapy.
- *Adjuvant WBRT (after surgery or radiosurgery)* may cause early adverse effects (fatigue, alopecia, Eustachian tube dysfunction) and late neurotoxicity. Long-term survivors after WBRT frequently develop radiographic changes on computed tomography (CT) or magnetic resonance imaging (MRI), including cortical atrophy, hydrocephalus, and hyperintensity of the periventricular white matter in T2 and fluid-attenuated inversion recovery (FLAIR) images. Up to 11% of patients receiving hypofractionated schedules of radiotherapy (size fraction of 4 to 6 Gy) have clinical symptoms such as memory loss progressing to dementia, frontal gait disorders, and urinary incontinence.

Contraindications

Contraindications

In patients who suffer from epileptic seizures and need a concomitant treatment with chemotherapeutics, enzyme-inducing antiepileptic drugs (EIAEDs) should be avoided.

Qualifying Statements

Qualifying Statements

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list, and all guideline papers go to national societies, national ministries of health,

World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, Heimans J, Hildebrand J, Hoskin P, Kalljo M, Krauseneck P, Marosi C, Siegal T, Vecht C. Brain metastases. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 437-45. [59 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Jul (revised 2011)

Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

Source(s) of Funding

European Federation of Neurological Societies

Guideline Committee

European Federation of Neurological Societies Task Force on Brain Metastases

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

None of the members of the Task Force, including the chairperson, had any form of conflict of interest.

Guideline Status

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This guideline updates a previous version: Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, Heimans J, Hildebrand J, Hoskin P, Kalljo M, Krauseneck P, Marosi C, Siegal T, Vecht C. EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. Eur J Neurol 2006 Jul;13(7):674-81.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies (EFNS) Web site .

Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on April 6, 2007. The information was verified by the guideline developer on May 25, 2007. This summary was updated by ECRI Institute on June 26, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This summary was updated by ECRI Institute on December 26, 2008 following the FDA advisory on Innohep (tinzaparin). This summary was updated by ECRI Institute on February 20, 2012. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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